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Cytokine profiles of plasma and intestinal mucosa can differentiate between wild-type and APC$^{min/-}$ mice and between different dietary fatty acids

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Chronic inflammation is considered to be a risk factor for colorectal cancer (CRC) that may be exacerbated by the consumption of *n*-6 fatty acids and ameliorated by the dietary long chain *n*-3 fatty acids DHA and EPA[1,2]. We have recently reported that diets high in fish oil-derived *n*-3 fatty acids reduce small intestinal tumour size but not number in the APC$^{min/-}$ mouse model[3]. However, in contrast to our earlier observations in other animal models of CRC[4] this affect did not appear to be linked to levels of mitosis or apoptosis. The aim of the analysis reported here was to investigate links between cytokine expression and dietary fatty acid intake in the above study.

Sixteen APC$^{min/+}$ mice and 16 wild-type mice were allocated to either a fish oil (FO), palm oil (PO) or corn oil diet (CO) with 25% energy as fat (normal rodent diet is 12.5%) for 10 weeks from weaning. Blood samples were collected under anaesthesia, and following cervical dislocation the intestine was removed. A total of 21 cytokines were measured using Luminex technology, in plasma, distal small intestine (SI) and colon. The levels of cytokine expression were compared individually by ANOVA and patterns of expression analysed using principal components analysis (PCA).

In the distal SI, PCA was able to distinguish between wild-type and APC$^{min/+}$ mice fed FO, where the first principal component explained 75% of the variation and in the PO group PC1 explained 62% of the variation. KC (mouse equivalent to IL-8) was increased in all APC$^{min/+}$ mice but only IL-15 was increased ($P = 0.02$) and only IP10/CXCL10 decreased ($P = 0.02$) just in those fed FO. MIG/CXCL9 was significantly higher ($P = 0.04$ and $P < 0.01$) and IL-12p40 lower ($P < 0.01$ and $P = 0.04$) in both CO- and FO-fed APC$^{min/+}$ mice. These differences were not apparent in the PO group, not because of diet effects in the APC$^{min/+}$ mice but because the cytokine levels in the wild-type mice fed PO were more like those in APC$^{min/+}$ mice. The only exception to this was IL-15 in the FO-fed mice. Only GMSCF, IL-1β, IL-6, TNFα and MCP-1 were measured in the colon with IL-6 being decreased in both CO- and FO-fed mice ($P = 0.04$). Plasma cytokine levels were much less affected by the presence of the APC mutation. CO increased plasma IL-1α compared to FO and PO ($P = 0.05$), while FO increased IL-5 ($P = 0.01$), IL-6 ($P = 0.01$) and MCP-1/CCL2 ($P < 0.01$).

The most marked effects of the APC mutation were seen in the SI, the site where most tumours are found in this model. The raised levels of IL-15 in mice fed FO may explain the reduced tumour size in this group as this cytokine is associated with increased natural killer cell activity. MIG/CXCL9 and IP10/CXCL10 both signal through CXCR3, but the increase in MIG/CXCL9 was more significant and thus the expected effect of this change would be an increase in chemotactic signalling. Further bioinformatic analysis of the observed changes in cytokines in relation to apoptosis, mitosis and tumour size is currently being carried out. We expect this to provide greater insight as to the significance of the observed changes, but it is already apparent that FO can modify the patterns of mucosal cytokine expression in a potentially beneficial manner.

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